tenth dorsal to the first lumbar segments on the left side there was swelling, with cavity formation, occupying almost exclusively the gray matter; patchy degeneration of the posterior columns, especially in the lower cervical region.

The patient was admitted to Bellevue Hospital, August 24, 1904, where he remained until December 13, 1904. The state of the blood during this time is shown in Fig. 1.

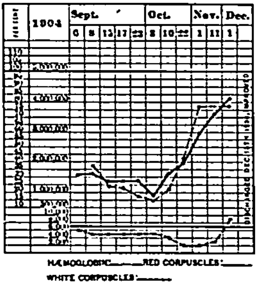

FIG. 1.—The blood chart of Case I in 1904. Microscopic examination showed the characteristic features of pernicious anemia. The highest lymphocyte count (October 3, 1904) was 37 per cent., with a polynuclear neutrophile count, on the same date, of 55.6 per cent. Normoblasts were usually present; and reached 34 in a slide on October 10, 1904. At this time 9 megaloblasts were also found, but thereafter nucleated red cells were not seen.

The following is a brief summary of the notes made on admission: A history of syphilis with initial lesion nine years previously, and excess in alcohol. Two months before admission the feet and legs swelled. Headache, dizziness on rising from recumbent position, burning pain across the abdomen, numbness in the hands and feet, and shortness of breath. Compelled on account of weakness to give up work. On examination, the diagnosis of pericarditis, chronic valvular disease, and chronic catarrhal gastritis was made, in addition to that of pernicious anemia. The stools were negative for parasites and ova. The gastric analysis showed a total acidity of 0.00073; free organic acids and salts, 0.00063; combined and free hydrochloric acid, 0.

There was nothing referable to the nervous system except persistent headache, pain over the chest and abdomen, and numbness on the left side of the body extending to the left side of the face, tongue, and lips. This latter condition occurred in paroxysms of about six minutes' duration. No objective disturbance of the nervous system was noted.

On December 13, 1904, he was discharged improved. Between this date and January 12, when he was finally admitted to the City Hopital, he was under observation at the Metropolitan Hospital, Cornell Dispensary, and, for a brief period (one week for alcoholism) at the City Hospital. The records from these clinics show that cardiac insufficiency with valvular disease, and alcoholism with its accompanying gastro-intestinal disturbances, were the chief features. Weakness in the legs is the only note suggestive of any nervous affection. He labored in a drop-forge and coal yard and at other occupations requiring considerable muscular effort.

When admitted to the City Hospital the condition of his blood was as shown in Fig. 2.

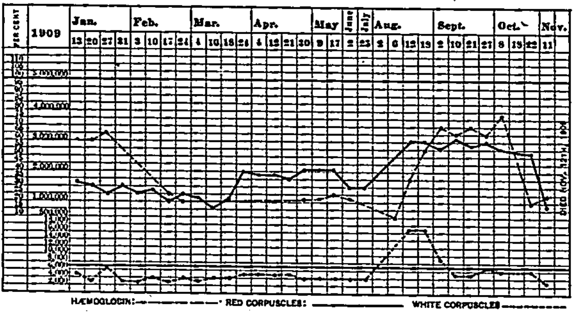

FIG. 2.—The blood chart in Case I in 1909. The microscopic examination was typical of pernicious anemia. The highest lymphocyte count was 45 per cent. (July 25, 1909); the polynuclear neutrophile count, at the same time, was 38 per cent. Nucleated red cells were a constant feature, megaloblasts preponderating.

The following is a summary of the clinical notes:

Male, aged thirty-eight years. Complains of pain in the chest, dyspnœa, dizziness, faintness, and tingling in feet and legs History of sore tongue and bleeding gums of some months' duration. Examination showed a well-nourished man, with good amount of adipose tissue; yellowish skin. The heart showed signs of chronic valvular disease with acute incompetency. The liver and spleen were palpable. Other signs were those of profound anemia. At no time were there any symptoms or signs referable to the nervous system. The pupillary reflexes were active and knee-kick was present. No paresthesias were noted. Shortly before death the patient was walking about the ward. Up to a month before his death the blood (Fig. 2) had been steadily rising, reaching nearly as high as it did five years before, when he had been able to return to heavy labor. A month prior to death, however, the erythrocyte count fell rapidly from 3,800,000 to 1,500,000. In view of the extensive changes in the cord found postmortem, all these clinical points are of considerable significance. Intestinal parasites or ova were not found. There was absence of free and combined hydrochloric acid.

The following notes are selected from those made between July 10, 1909 and November 12, 1909, the date of death:

July 4, 1909. Has been vomiting a great deal, takes little nourishment; restless at night; dyspnœa; moderate cyanosis; heart irregular; pallor much more marked; cheeks colorless; irrational at times; asthenia extreme; sways slightly when he walks and requires assistance, but presents no peculiarity of gait; confined to bed.

July 10. Condition gradually improving; nausea and vomiting stopped; appetite returned; cyanosis disappeared; dyspnœa slight.

August 8. Improvement more marked (Fig. 2).

August 30. Improvement steady; able to walk about unassisted; marked improvement in blood (Fig. 2.)

September 22. Six or seven fluid stools daily for two days. Temperature 102°; nothing in the physical examination to account for the temperature; no blood or mucus in the stools.

September 29. Stools and temperature normal; general condition good.

October 31. Up and about ward since note of September 29, but to-day he says he has not been feeling well for ten days; weakness, dizziness; roaring in head; precordial pain; loss of appetite; skin has undergone striking change in color (yellower); returns to bed.

November 6. Is very dizzy, even in bed.

November 11. Asthenia very marked; lemon tint of skin very marked. Patient is drowsy and he gives an expiratory grunt; answers questions rationally. There is a jugular impulse synchronous with the carotid. Cardiac impulse distinctly visible and seen over a large area, but feeble to the touch. A systolic murmur to the right of the sternum different in character from that heard at the apex. Liver does not pulsate but is readily palpable. Examination of feces negative. Urine examination showed occasional hyaline casts; faint traces of albumin; specific gravity between 1012 and 1030. Examination of gastric contents made on September 8, 1909 showed no free or combined hydrochloric acid.

November 11. The patient died.

Postmortem (ten hours after death): A well developed male, rather poorly nourished and apparently about forty years of age. The skin presented a uniform lemon yellow color. The sclerotics and external mucous membranes were not pigmented. There was a considerable degree of gingivitis and the tongue was also very furred, but neither condition appeared more marked than that commonly found at autopsy in cases which have had other causes of death. The teeth were in fairly good condition. There were no scars, skin eruptions, or hemorrhages, superficially anywhere, nor were the surface lymphatic glands or the thyroid enlarged. The left pleural cavity contained 4 ounces of clear fluid, and the right 10 ounces of a similar fluid. The subcutaneous fat was rather less than normal in amount, and the muscles were of a bright dark brownish-red color. The peritoneal cavity contained no excess of fluid, and there was no chronic peritonitis. The pericardium contained 4 ounces of clear, straw-colored fluid and showed no evidences of pericarditis.

The heart weighed 400 grams, was soft and flabby, and all its chambers were slightly dilated. The tricuspid orifice admitted four fingers and the mitral three. There was no deformity or acute endocarditis of the valves. The right side was relatively more dilated, and the myocardium of the right ventricle was slightly hypertrophied. In the myocardium of the left ventricle, just under the endocardium and particularly near the mitral orifice was a typical thrush-breast appearance from fatty degeneration.

The lungs were slightly pigmented and œdematous. They were also uniformly somewhat emphysematous. The bronchial and mediastinal lymph glands were not enlarged.

The mesenteric and peritoneal lymph glands were all slightly enlarged and of a pinkish white-color. Microscopically they showed a considerable proliferation of the lymphoid cells, many having become somewhat swollen and often containing some brown pigment.

The intestines were somewhat collapsed throughout and were rather transparent, and their lining mucosa appeared very smooth and atrophied. Microscopically the glands were considerably degenerated and in many parts disintegrated to a considerable extent from postmortem changes. In parts also there were some small aggregations of inflammatory large mononuclear cells.

The stomach was slightly dilated, its walls thin and its lining mucosa smooth and atrophic. Microscopically this mucosa showed some considerable atrophy and degeneration of the glands, but no marked inflammatory processes.

The liver weighed 1450 grams, was very soft in consistence and of a brownish-yellow color. It gave a very marked Prussian blue reaction for iron. Microscopically it showed an extensive fatty degeneration, particularly located in the inner half of the lobules, around the central veins. In these areas the liver cells were very extensively necrotic, while those at the periphery were much better preserved. No vascular thrombosis could be observed. There was also a very marked deposit of pigment granules in the liver cells, especially toward the periphery of the lobules. The greater part of this pigment gave the reaction of hemosiderin and with prolonged staining practically all the pigment gave the Prussian blue reaction. The lining endothelium of the intralobular capillaries in occasional places showed a very marked swelling, proliferation, and specialization, the formation of blood constituents being in these places particularly easy to observe. There was also in considerable numbers, coarsely granular eosinophile cells, with all sizes and types of nuclei, but mostly small, and with one or several nuclei like those of a normoblast. These were attached to the walls of the capillary, as a rule, but also occasionally lay free.

The bile passages were clear. The gall-bladder contained a small amount of dark, inspissated bile, but no stones.

The spleen weighed 450 grams, was considerably enlarged, soft in consistence, and dark brownish-red in color, the Malpighian bodies not appearing evident. It gave grossly a slight Prussian blue iron reaction. Microscopically it showed a rather atrophic appearance of the Malpighian bodies. The sinuses all appeared somewhat distended and for the most part contained a large proportion of nucleated cells. Some of these cells resembled megaloblasts and some, less frequently, were normoblastic in type. Many of these cells had the appearance of developing locally, rather than of being collected from the general circulation. As in the liver, with considerable frequency, coarsely granular, eosinophile cells could be seen, of all shapes, but mostly with one or several small normoblastic-like nuclei.

The suprarenal glands were considerably atrophied.

The kidneys were slightly enlarged and of a pale, brownish-yellow color. They gave a very distinct and rapid iron reaction, chiefly in the cortex. Microscopically there was a very extensive fatty degeneration of the secreting tubules, and also a very considerable deposit of iron-containing pigment.

The bladder and prostate showed no special change.

The pancreas also appeared well preserved.

The bone marrow in the centre of the shaft of the femur had a uniform, dark raspberry color. Microscopically the fat cells had almost all been replaced by a new cellular development. These new cells were mostly erythroblastic, there being megaloblasts and normoblasts in very large numbers. There was also a very considerable leukoblastic change, as there was very numerous collections of faintly acidophile myelocytes in all stages of transition. There were relatively only a very few eosinophile myelocytes.

The mastoids and tympani appeared healthy.

The cerebral meninges showed no abnormality and the vessels at the base of the brain were well preserved. The brain was firm and in good condition. It was œdematous and showed no other gross lesion. Microscopically in the cortex, in several parts examined, and in the pons, no special lesion could be observed. The medulla for the most part showed no abnormalities, but several very small patches of degeneration in the posterior columns, in the extreme lower part. The nuclei of the medulla appeared well preserved.

The spinal cord presented somewhat extensive lesions. Although the autopsy was done ten hours after death, the brain and cord were removed from the body thirty-eight hours after this. Ten c.c. of 10 per cent. formalin, however, was injected in the usual site of lumbar puncture ten hours after death.

The membranes of the cord showed no abnormality nor grossly did the entering vessels or nerves. There was no excess of fluid within the membranes, discounting the small amount of formalin injected. The cord, with the exception of a small portion, in its entire course showed no gross change, there being no shrinking, deformity or softening, and was in a good state of preservation. This exception was between the level of the tenth dorsal and first lumbar segments where, for a distance of about 2 cm., it was very much swollen on the left side. The right side, opposite this, did not appear to be affected. There was no communication externally from the interior of this swelling and no discoloration or meningeal change over it. The vessels, however, were somewhat congested on the surface of this part. On section of this swollen area, there could be seen a very extensive destruction of the cord. A large space containing a clear fluid occupied a large part of the left side in this position. This space was not surrounded by any noticeable inflammatory reaction or sclerosis, yet it was rather well defined. It occupied almost exclusively the gray matter, and the process extended between the tenth dorsal and the first lumbar segments. In the upper and lower parts there was only a very small aperture in the gray matter, on the left side, and in the deeper part of the anterior horn. This cavity formation became gradually larger until it occupied a very large part of the gray matter on the left side.

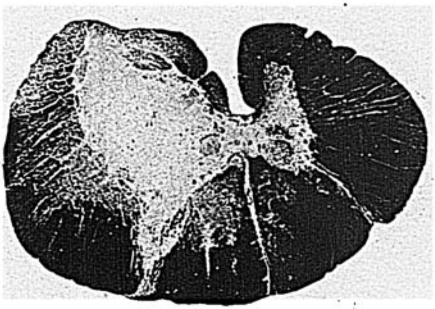

FIG. 3.—The spinal cord in Case I, showing extensive destruction of the gray matter of the left side.

In the middle portion, opposite the twelfth dorsal segment, the gray matter was completely destroyed and the cavity extended out and laterally almost to the surface of the cord (Fig. 3). In all its length this process was located chiefly in the anterior horn, which, as the cavity became larger, destroyed it almost completely, before the posterior horn was much affected, and even when the cavity was relatively very large, the posterior part of the posterior horn largely escaped damage (Fig. 4). In all situations this lesion caused, according the to size of the cavity, a swelling of the gray matter on the left side, particularly of the anterior horn. Where the cavity grossly could not be seen, as in the upper and lower extremities of this process, the gray matter on the left side, particuliarly anteriorly, appeared swollen (Fig. 5).

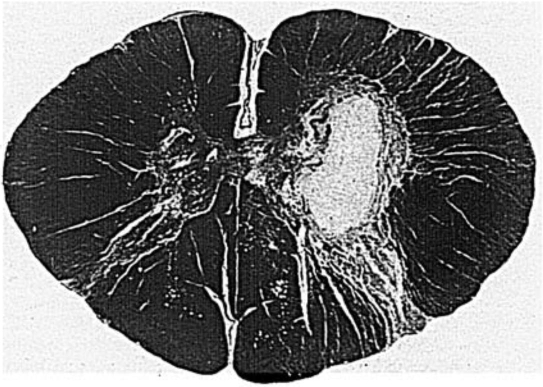

FIG. 4.—The spinal cord in Case I, showing destruction and cavity formation in the gray matter of the left side. (The specimen has been reversed.)

Microscopically there was a patchy degeneration in the posterior columns. In the lower cervical regions it affected irregularly a large portion of both Goll's and Burdach's tracts (Fig. 6). In the dorsal region the degeneration was not nearly so extensive, but there were patches in the interior of the posterior columns in the entire course of the dorsal cord and upper lumbar segments, becoming less extensive from above downward. In the sacral and lower lumbar regions, no degeneration existed. In these areas there was a disintegration of the nerve fibrils, and also a considerable amount of replacement gliosis. There were numerous large vacuoles, sometimes containing remnants of degenerated nerve fibrils. In these same degenerate areas, however, always some healthy nerve fibrils remained and some also showing a homogeneous swelling of the myelin sheath, very often associated with disappearance or disintegration of the axon. There were, however, no evidences of inflammatory reaction. The other columns of the cord showed no degenerative changes. The ganglion cells in the gray matter showed no particular change beyond perhaps a slight excess of pigment granules. In the area of extensive destruction seen grossly, the tissues seemed

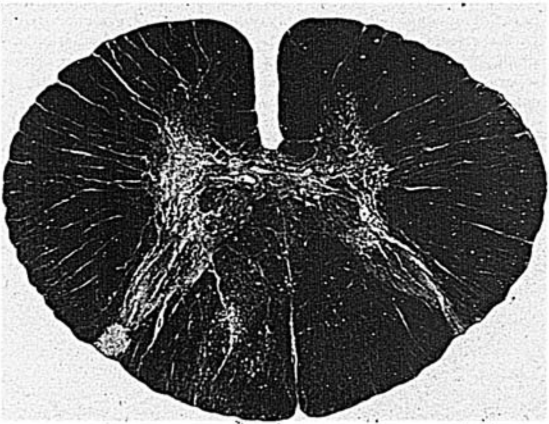

FIG. 5.—The spinal cord in Case I, showing swelling of the gray matter of the left side from œdematous separation of the tissues.

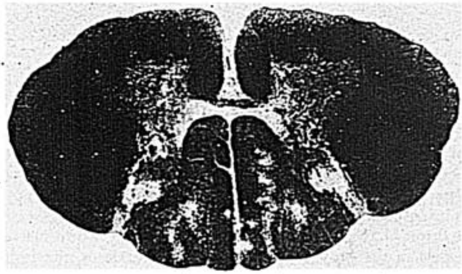

FIG. 6.—The spinal cord in Case I, showing patchy degeneration of the posterior columns.

more split up and distorted than necrotic. In those parts where the aperture appeared small in the gross, the tissues were simply separated apparently by fluid. There was very slight or no inflammatory reaction around the cavity. There were occasionally a few leukocytes, but no hemorrhage around or in the disintegrated part. The cavity contained only some clumps of granular debris. In the greater part of this lesion, where the cavity formation was small, the nerve cells and tissues of the gray matter were simply separated. Where the cavity was largest, the nerve cells of the entire anterior horn were largely destroyed, but this was only for a short distance, and even in this place the cells of Clark's columns and of the posterior root were comparatively unaffected. All the vessels in the affected area on the left side were surrounded by a wide space, as if from œdema, and several of the smaller capillaries and veins, especially just above where the cavity was largest, showed recent thrombi (Fig. 7). The pial vessels in the white matter and the vessels in the gray matter at the same levels on the right side did not show any congestion or œdema. In this case, although postmortem processes may have to some extent influenced the appearances presented, yet it seemed to be the result of thrombosis of some of the small branches of the anterior spinal veins, with resulting effusion of fluid, with separation of the tissues, and some mechanical destruction of the related structures in the gray matter.

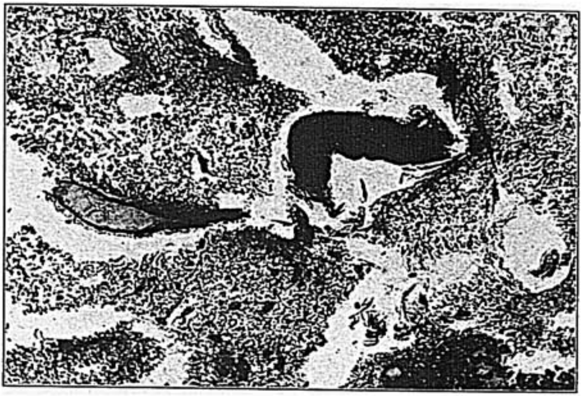

FIG. 7.—The spinal cord in Case I, showing the microscopic appearances of the gray matter in the section shown in Fig. 6. The small veins are surrounded by distended perivascular spaces and one of them is filled by a recent thrombus.

Case II.—*Under observation three years; symptoms and signs of pernicious anemia; headache; dizziness; tingling and numbness in the hands and feet for two and one-half years; six months before death there was spastic paraplegia and paresthesia; at the postmortem the characteristic changes of pernicious anemia; degeneration of the posterior and lateral columns of the spinal cord; extensive degeneration of the posterior columns and crossed pyramidal tracts, chiefly from the midcervical to the lower dorsal regions; slight degeneration of the direct pyramidal tracts.*

Case II presented the symptoms and signs of pseudocombined sclerosis (Henneberg). The nervous manifestations were more or less present during the three years he was under observation, but when admitted to the New York Hospital, the diagnosis of pernicious anemia was recorded as the primary disease, and he was assigned to the Medical Division, while two and a half years later, when admitted to the City Hospital, the case was regarded as primarily neurological, and he was assigned to that division of the hospital. The postmortem examination revealed the characteristic changes of pernicious anemia, and in consequence his early record was traced.

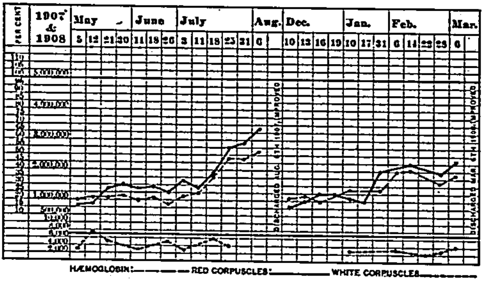

Fig. 8.—The blood chart of Case II. The microscopic examination was typical of pernicious anemia. The highest lymphocyte count was 58 per cent. (July 18); the polynuclear neutrophile count on the same date was 25 per cent. A striking feature was the absence, for the most part, of megaloblasts. Normoblasts were constantly observed, although not in great numbers.

He was admitted to the New York Hospital, May, 1907. He denied having had syphilis, but gave a history of alcohol in excess up to three or four months previously.

Fig. 8 shows the blood condition on his two sojourns in the hospitals, from May, 1907 to March, 1908. There was slight fever, the temperature ranging between 100° and 101°. There were no marked disturbances of the nervous system found during this period. The following clinical notes are selected as indicating the condition of his nervous system at this time.

December 10, 1907. Knee-jerks not obtained.

January 7, 1908. Pain in chest, headache, tingling and numbness in hands and feet.

February 11, 1908. Taking short walks on the street.

On leaving the hospital he was able to work (hotel clerk) for three months, but had to give up on account of weakness, and a few months later he developed cramps in both legs. He was not confined to bed but sat at home, the weakness in the legs steadily increasing. This weakness continued to increase until August, 1909, when, on attempting to walk, he fell repeatedly.

In September, 1909, he was admitted to the City Hospital. On admission he was found unable to walk. Well-developed male, aged fifty-five years. Skin is lemon-color. Eyes negative; upper extremities normal. The lower extremities give exaggerated reflexes with spasticity. Skin hyperesthetic. Sensation to heat is lost below crest of ilium with exception of the inner surfaces of the thighs. The blood shows oligocythemia and nucleated red cells and anisocytosis.

November 23, 1909. Patient is drowsy and incontinent of urine. Complains of abdominal pain. Mental condition good.

December 1, 1909. Knee reflexes absent. Tactile sense greatly diminished in the lower limbs. Muscular atrophy marked and there is great loss of power. Subcutaneous œdema and numerous vesicles have appeared over both legs, and bedsores over hips and sacrum.

December 5, 1909. The patient died.

Postmortem (fifty-one hours after death): A well-nourished man, apparently sixty years of age. There was no œdema, scars, skin eruption, or hemorrhages. The skin was uniformly of a light lemon-yellow tint. The superficial lymphatic glands and thyroid were not enlarged. There was a moderate degree of gingivitis, and the teeth were considerably decayed. The superficial fat was found to be in considerable amount, and the skeletal muscles were of a dark brownish-red color. Both pleuræ were somewhat adherent posteriorly, but there was no fluid on either side. The abdomen showed no ascites or peritoneal adhesions. The pericardium contained a few cubic centimeters of a straw-colored fluid, but showed no evidence of pericarditis.

The heart weighed 425 grams, was very soft and flabby, and slightly dilated in all its chambers, particularly on the right side. There was in this case no thrush-breast appearance from fatty degeneration in the left ventricle, but the myocardium of the whole heart was evidently very considerably degenerated. The aorta and larger vessels were very well preserved. The lungs were œdematous and very emphysematous. The mediastinal, bronchial, mesenteric, and retroperitoneal lymph glands appeared pale white on section, and did not show any special enlargement.

The intestines were somewhat dilated and apparently rather atrophic. Microscopically a very marked change was evident. The lymphoid elements were markedly hyperplastic and there were also evidences of extensive chronic inflammatory processes. The glands were largely degenerated and in many places had disappeared, their places being taken by young fibrous tissue or aggregations of large, frequently phagocytic, mononuclear cells. There was practically no pigment deposit in this situation.

The stomach was slightly dilated and its mucosa smooth and atrophic-looking. Microscopically there was considerable atrophy and degeneration of the glands, in parts also, small hyperplastic lymphoid aggregations, and also widespread subacute inflammatory processes.

The liver weighed 1600 grams, was very friable, and of a dark brownish color. It gave a very rapid and very pronounced Prussian blue iron reaction. Microscopically it showed a very widespread fatty degeneration, not being particularly localized in the central parts of the lobules, as it was in Case I. There was also a very considerable deposit of iron-containing pigment in the liver cells throughout the lobules, and also in all the tissues of the organ, including the lining cells of the vessels. In certain places the lining cells of the capillaries in the lobules were swollen, forming small groups, but no definite appearances of reformation of blood cells were observed. The gall-bladder contained a small amount of orange-colored bile, but no stones. The bile passages were free.

The spleen weighed 325 grams. It was slightly enlarged, very soft, and of a dull red color. The Malpighian bodies were not evident. It also gave a very pronounced Prussian blue iron reaction. Microscopically the Malpighian bodies were large and irregularly defined, evidently somewhat hyperplastic. All the sinuses appeared to be filled with nucleated cells. These cells were very frequently the seat of a deposit of hemosiderin. Frequently some small clumps of nucleated, hemoglobin-containing red cells of normoblastic, but more frequently of megaloblastic type, could be seen adhering to the walls of the sinuses. It seems as if there were, then, some little regeneration of blood cells taking place in these sinuses from endothelial proliferation and specialization.

The kidneys were slightly enlarged, pale, flabby, and of a pale yellow, slightly brownish color. They gave typically in their cortical parts a very bright Prussian blue reaction. Microscopically there was a very extensive fatty degeneration involving particularly the cells of the secreting tubules.

In none of these organs was there any amyloid change. The bladder and prostate were negative. The pancreas also showed no abnormalities, except slight atrophy.

The bone marrow in the centre of the shaft of the femur was dark red in color. Microscopically the erythroblastic and leukoblastic change was not so marked as in the first case, yet very largely the fat spaces had been replaced by aggregations of regenerating blood cells. There were in these places numerous megaloblasts and normoblasts, also frequent myelocytes in all stages of transition to polymorphonuclear cells. In this case also coarsely eosinophile cells could only very occasionally be observed.

The mastoids showed no signs of suppuration.

The large vessels at the base of the brain were very well preserved and the membranes showed no abnormalities, grossly or microscopically. The brain was slightly œdematous. It showed on minute examination no gross lesion. Microscopically the cortex of the Rolandic and frontal areas, in the pieces examined, showed no special change and the internal capsule, crura, and pons, likewise.

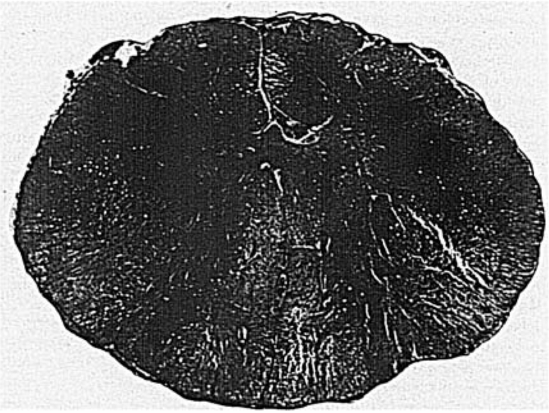

FIG. 9. The spinal cord in Case II, showing combined degeneration of the posterior and lateral tracts; the direct pyramidal tracts are also considerably degenerated.

In the lower part of the medulla there was a slight patchy degeneration in the lateral and posterior tracts. In the region of the decussation of the pyramids, it existed only in irregular streaks, and above this no change could be seen. The nuclei of the medulla were not especially degenerated.

The membranes of the cord were in good condition, as also were the nerves and vessels relating to it. There was no excess of fluid in the spaces surrounding the cord. The cord itself was firm, and in a fairly good state of preservation. Grossly it showed no deformity or local shrinkage or softening, but there was on section a slightly darker appearance than normal of the posterior and lateral columns.

Microscopically it was evident that throughout practically the entire length of the cord there was a very extensive degeneration of the posterior and lateral columns (Fig. 9). This degeneration was most extensive in the lower cervical region, becoming less marked above this, and gradually also below it. In the sacral region, it was only very slightly evident after the first segment. In all situations it was irregular, not being confined to any well circumscribed area, and not strictly adhering to the cord tracts. The posterior column lesion was rather better defined, and apparently of older standing than was the change in the lateral columns; and the lateral column lesion became less extensive and less complete in the lumbar region than the corresponding change in the posterior columns. There were, however, degenerative changes noticeable in the lateral columns as low as the lower lumbar region. Throughout the entire length of the degeneration in the posterior columns, and especailly in the dorsal region, the outer part of the column of Burdach, for a narrow strip along the posterior tract, was comparatively unaffected. The degeneration in the lateral columns did not exclusively affect the crossed pyramidal tract. The direct cerebellar and adjacent parts of Gowers' tract were generally irregularly involved. The direct, or anterior, pyramidal tract was very irregularly affected, being degenerated for short areas on one or both sides.

The degeneration in all these situations, which was characteristically irregular, appeared as a disintegration of the nerve fibers with solution of the myelin sheaths. There was thus produced a vacuolated, somewhat reticulated, appearance. Even in the most degenerated areas some unaffected nerve fibrils remained, and many fibrils also had the appearance of a solid, homogeneous body, containing no central axon. There seemed to be no inflammatory reaction in these areas and relatively only a small amount of replacement gliosis. There were apparently no hemorrhages or inflammatory changes anywhere. The gray matter was intact throughout. Many of the ganglion cells showed some slight evidence of degeneration, probably postmortem in origin, and often were somewhat overpigmented, but there were no evidences of inflammation or of hemorrhage.

The vessels of the cord in general, and in the degenerated areas showed no particular abnormality, although several of the small arteries did occasionally show a slight degree of hyaline degeneration. In no situation was any process of endarteritis found.

These two cases illustrate two of the types of nervous-system involvement occurring in the course of pernicious anemia. In the first case, which had the longest and more pronounced history of anemia, the nervous symptoms were at a minimum and the posterior columns of the cord, particularly in the cervical region, alone showed degeneration, characteristically patchy in distribution. In the second case the nervous involvement, particularly in the later stages, overshadowed the anemia. Here the spinal cord presented very extensive, yet incomplete degeneration with slight replacement gliosis in the posterior columns, and also a similarly irregular but more diffuse degeneration in the lateral tracts, which, however, was a rather less complete and apparently somewhat more recent, process.

The nervous manifestations observed clinically in both cases did not quite correspond in severity with the extent of the pathological spinal cord lesions, a fact which has been repeatedly noted (Strümpell,[13] Dinkler,[14] etc). It bears repeating, however, that cases of combined sclerosis pass the neurologist without the gravity of the anemia which sometimes accompanies it, being appreciated. It is also true that the internist overlooks the fact that in pernicious anemia changes may be taking place in the cord, which only delicate tests by a skilled neurologist can detect. Most of the records bear out this statement.

The occurrence of changes in the nervous system, particularly what has been termed pseudocombined sclerosis, associated with pernicious anemia, has been very frequently and extensively described since the time of Lichtheim, in 1887, and has thus come to be a well recognized possible event. Such lesions in the spinal cord in pernicious anemia have been described by practically all observers, as an irregular degeneration or sclerosis in the posterior columns, with, in many cases, a similar associated process in the lateral, particularly pyramidal, tracts. Kast[15] and Alt,[16] however, have described local changes in the medulla in leukemia, and Dana and others have noted in the spinal cord localized areas of softening from vascular obstruction. The clinical symptom complex now termed pseudocombined sclerosis is well reviewed in the publications of Collier, Batten, and Russell,[17] in 1909, and Siemerling,[18] in 1909.

This combined tract degeneration as the advanced stage of nervous involvement and, at least, degenerative changes in the posterior columns, have been noted with identical appearance in a great variety of chronic, toxic, cachectic, or anemic conditions. Dana gives 10 per cent. as the number of cases described as combined sclerosis which were due to pernicious anemia. Of Taylor's[19] 50 cases, 6 had pernicious anemia. Besides this there have been

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[13] Ueber eine bestimmte Form der primären combinirten Systemerkrankung des Rückenmarks, Arch. f. Psychiatrie, 1886, xvii, 217.

[14] Ueber die klinischen Verlauf und die anatomischen Veränderungen bei progressiver perniciöser Anämie mit Spinalstorungen, Neurol. Centralbl., 1902, xxvi, 620.

[15] Beiträge zur Pathologie der Leukämie, Ztschr. f. klin. Med., 1895, xx, 181.

[16] Sectionsbefund eines Falles von Morbus Ménièrei (Leukämie), Wien. med. Woch., 1896, xlvi, 919.

[17] Subacute Degeneration of the Spinal Cord, Brain, 1900, xxiii, 39.

[18] Rückenmarkserkrankung und Psychose bei perniciöser Anämie, Arch. f. Psychiatrie, 1909, xlv, 567.

[19] Nervous Symptoms and Morbid Changes in the Spinal Cord in Certain Cases of Profound Anemia, Medico-Chirurg. Trans., London, 1895, lxxxviii, 151.

reported cases dependent on chronic ergot poisoning, Tuczec,[20] Redlich[21]; carcinoma; Lubarsch,[22]; diabetes, Williamson,[23] Sandmeyer[24]; septicemia and ulcerative endocarditis, Nonne[25]; pellagra, Tuczec,[26] Marie,[27] Belmondo[28]; lathyrism; nephritis; malaria, Mayer[29]; shock; lead-poisoning, v. Monakow,[30] Oppenheim;[31] arsenic poisoning, Dana;[32] phosphorus poisoning; Addison's disease, Fleiner,[33] Brauer,[34] Kahlden;[35] tuberculosis, Summa;[36] syphilis; diphtheria, Bicheles,[37] Priesz;[38] typhoid fever and influenza, Redlich; scarlet fever, Billings;[39] chronic jaundice, Minnich;[40] chronic alcoholism, Braun,[41] Nonne,[42] Vierordt,[43] Redlich; leukemia, Kast, Müller,[44] Alt, Nonne,[45] Bloch and Hirschfeld;[46] bothriocephalus anemia, Lichtheim; tetanus, Bonome,[47] Orr and Rows;[48] after extirpation of the adrenals experimentally, Tizzoni;[49] leprosy, Looft;[50] acute insanity; etc. Such a list offers a strong evidence in support of a toxic factor as the primary agent in producing the tissue changes. Old age has also been ascribed as a cause of similar spinal cord degeneration (Sanders,[51] Naka,[52] and others), changes having been noted particularly in the posterior columns. Leyden[53] discussed this problem of cord involvement in old age, and concluded that it was a process secondary to some ganglion cell atrophy, rather than a primary white matter degeneration. Ribail[54] traced the condition found in certain old subjects to a thickening of the membranes with the resulting local sclerosis, and Démange[55] concluded that the spinal cord lesions in old age results from a thickening around and of the walls of the vessels which, however, causes appearances differing widely from any system of sclerosis. Nonne, in ten cases of senile marasmus, found a glial thickening and nerve fiber atrophy in the posterior columns, and to a slight extent although less definite, in the lateral tracts. He also observed a non-inflammatory thickening of the vessels limiting their lumen. It might also be mentioned, although our observations are not sufficiently numerous to be conclusive, that of the cord lesions from four extremely old and very atrophied subjects, who presented at autopsy no other lesions than extreme general atrophy and some little arteriosclerosis, none showed areas of degeneration anywhere in the gray matter of the cord. The vessels occasionally did show a slight hyaline thickening but were not surrounded by any nerve tissue degeneration or glial proliferation. The nerve fibrils as a whole, seemed somewhat atrophied, but the cords were all remarkably and relatively well preserved. The part played by defective nutrition, *per se*, in the production of degeneration in the cord is doubtful. Oppenheim denies it, and Pugibet[56] did not find any marked change in the cords of subjects dead from chronic dysentery. Experimentally, the results of attempts to produce similar degeneration in the cord, have not been uniform. Grünfeld[57] failed to produce any result on the cord by means of ergot injections. Brauer, however, obtained definite lesions in the cord as the result of alcohol administration. Von Voss[58] produced severe anemia in animals, but was unsuccessful in producing any definite cord lesions. It must then be held that any toxic process, if sufficiently severe and prolonged, may cause a degeneration in the posterior tracts or even a development of a widespread degeneration. Gordon[59] and others have made the distinction, although not widely credited, that the hemolyzed substances set free by the action of a toxin of the blood are responsible for the changes in the cord.

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[20] Ueber die Veränderungen im Centralnervensystem, special in den Hinterstränge bei Ergotismus, Arch. f. Psychiat. 1882, xiii, 99.

[21] Ueber einige toxische Erkrankungen der Hinterstränge des Rückenmarks (Ergotismus, Pellagra, Infektionskrankheiten, chronischen intoxicationen und bei den Polyneuritis, perniciösen Anämie, Leukämie, Diabetes, Addison'sche Krankheit, etc.), Centr. f. allg. Path., 1896, vii, 985.

[22] Hyperplasie und Geschwülste (Bedeutung des Carcinoms für den Gesamtorganismus), Lubarsch-Oestertag's Ergebnisse, etc., 1895, ii, 519.

[23] Changes in the Posterior Columns of the Spinal Cord in Diabetes Mellitus, Brit. Med. Jour., 1894, i, 398.

[24] Beitrag zur pathologischen Anatomie des Diabetes Mellitus, Deut. Arch. f. klin. Med., 1892, 381.

[25] Rückenmarksuntersuchungen in Fallen von perniciösen Anämie, von Sepsis, und von Senium, etc., Deut. Ztschr. f. Nervenheilk, 1898-99, xiv, 192.

[26] Klinische und anatomische Studien über die Pellagra, Berlin, 1883.

[27] De l'origine exogène ou endogène des lésions du cordon postérieur étudiées comparativement dans le tabes et dans le pellagra, Sem. méd., 1894, xiv, 17, 28.

[28] Le alterazioni anatomishe del midollo spinalle nella pellagra, Riforma med., Napoli, 1889, v, 1532.

[29] Oppenheim's Diseases of the Nervous System, p. 159.

[30] Zur pathologischen Anatomie der Bleilähmung, Arch. f. Psych., 1880, x, 495.

[31] Zur path. Anat. der Bleilähmung, Arch f. Psych., 1885, xvi, 476.

[32] On Pseudotabes from Arsenical Poisoning, with a Consideration of the Pathology of Arsenical Paraylsis, Brain, 1886, v, 456.

[33] Ueber die Veränderungen des sympathetischen und cerebrospinallen Nervensystems bei zwei Falle Addison'sche Krankheit, Deut. Ztschr. f. Nervenheilk., 1891-92, ii, 265.

[34] Beitrag zur Lehre von den anatomischen Veränderungen des Nervensystems bei Morbus Addisonii, Deut. Ztschr. f. Nervenheilk., 1895, vii.

[35] Ueber Addison'sche Krankheit, Ziegler's Beiträge, 1891, x, 494.

[36] Ueber degenerative Veränderungen in Rückenmarke bei chronischer Lungenschwindsucht, Inaug. Diss., Freiburg, 1891.

[37] Post-diphtheritische Lähmung (Degeneration in die Rückenmarkssträngen und hinter Wurzeln), Arb. a. d. Inst. Obersteiner Wien, 1894.

[38] Beitrag zur Anatomie der Diphtheritischen Lähmung, Ztschr. f. Nervenheilk., 1894, vi, 95.

[39] The Changes in the Spinal Cord and Medulla in Pernicious Anemia, Shattuck Lecture, Boston, 1902.

[40] Zur Kenntniss der im Verlaufe der perniciösen Anämie beobachteten Spinalerkrankungen, Ztschr. f. klin. Med., 1892, xxi, 25, 246.

[41] Ueber die experimentelle durch chronische Alcoholintoxication hervorgerufenen Veränderungen im centralen und peripheren Nervensystem, Inaug. Diss., Tübingen, 1899.

[42] Klinische und anatomische Untersuchung eines Falles von Pseudotabes alcoholica, Jahrg. d. Hamb. Staatskrankenanst, 1892, ii, 91; Anatomische Befunde im Rückenmark bei Alkoholismus Chronicus Gravis, Deut. med. Woch., 1907, xxxiii, 166.

[43] Degeneration der Goll'schen Stränge bei einem Potator, Arch. f. Psych., 1886, xvii, 365.

[44] Ueber Veränderungen des Nervensystems bei Leukämie, Inaug. Diss., Berlin, 1895.

[45] Ueber Degenerationsherde in der weissen Substanz des Rückenmarks bei Leukämie, Deut. Ztschr. f. Nervenheilk., 1896-97, x, 165.

[46] Zur Kenntniss der Veränderungen an Centralnervensystem bei der Leukämie, Ztschr. f. klin. Med., 1900, xxxix, 32.

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[47] Sulla alterazione del midollo spinale nel tetano, Arch. per le sc. med., Torino, 1801, xv, 15

[48] A Clinical and Experimental Investigation into the Lymphogenous Origin of Toxic Infection of the Central Nervous System, Brit. Med. Jour., 1907, i, 987.

[49] Ueber die Wirkung des Extirpation des Nebennieren auf Kanninchen, Ziegler's Beiträge, 1889, vi, 3.

[50] Beitrag zur pathologischen Anatomie des Lepra anesthet. insbesondere des Rückenmarks, Virchow's Archiv, 1892, cxxviii, 215.

[51] Alters Veränderungen in Rücknemark, Ztschr. f. Nervenheilk, 1900, xvii, 369.

[52] Die pathologische Anatomie des senilen Rückenmarks, Arch. f. Psych., 1906-07, xlii, 604.

[53] Die senilen Processe im Rückenmarkkrankheiten, 875, ii, 42.

[54] Observations pour servir à l'histoire de l'arachnitis et de la lepto-méningite spinale chronique—sclérose médullaire secondaire, Gaz. méd. de Paris, 1885, ii, 25, 57.

[55] Contribution à l'étude des scléroses médullaires d'origine vasculaire, Rev. de méd., 1884, 753.

[56] Des paralysies dans la dysentèrie et la diarrhée chroniques dans les pays chauds, Rev. de méd., 1888, viii, 110.

[57] Zur Frage ueber die Wirkung des Mütterkorns und seiner Bestandtheile auf das Rückenmarks der Thiere, Arch. f. Psych., 1890, xxi, 618.

Clinically, from the records available, it seems impossible to associate the extent of the cord lesion with the degree of anemia. It seems, however, reasonable to infer than when the tissues are fed by the altered blood of these anemic states, a condition analogous to ischemia exists and at such times changes in the nervous system would be likely to begin or extend. It would seem, therefore, that when the blood conditions are at their severest the most critical neurological examination should be made and repeated at frequent intervals.

In the evolution of the literature of the spinal cord changes in pernicious anemia, several different pathological processes have been described as being the essential etiological factor. Thus, coalition of multiple small areas of hemorrhage to form a tract sclerosis was advocated by many of the earlier writers, Teichmüller,[60] Minnich, van Noorden,[61] Petrén,[62] etc. Myelitis was the essential process according to Nonne.[63] Boedecker and Juliusberger,[64] Marie, Rothman,[65] etc., described it as endogenous, being the sequence of an involvement of the ganglion nerve cells. Thickening of the vessel walls with resulting defective nutrition of the cord was considered by Nonne, Minnich, Redlich,[66] and others. It has also been suggested by Schmaus,[67] and others that the immediate destruction of the medullary sheaths and degeneration of the neuraxons is dependent on lymph stasis due to impoverished condition of the blood and its excess in lymph elements. All these various conditions could not, for obvious reasons, be responsible for the appearance found in the cord in pernicious anemia, nor could any evidences of such processes be observed in either of our two cases. Excessive fatigue is also a very doubtful factor, as it has been shown that nerve fibrils are practically inexhaustible and certainly less so than the ganglion cells or muscles. The process, agreeing with the conclusions of most modern authors, appears to be that of a degeneration with more or less replacement gliosis, and this accounts best for its irregular, imperfectly systemic, and incomplete character.

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[58] Anatomische und experimentelle Untersuchungen über die Rückenmarks-Veränderungen bei Anämie, Deut. Arch. f. klin. Med., 1897, lxviii, 489.

[59] Histological Changes in the Spinal Cord in Pernicious Anemia, New York Med. Jour., 1909, xc, 80.

[60] Ein Beitrag zur Kenntniss der im Verlaufe der perniciösen Anämie beobachteten Spinalerkrankung, Deut. Ztschr. f. Nervenheilk., 1896, vii, 385.

[61] Untersuchungen über schwere Anämien, Charité Annalen, 1891-92.

[62] Bidrag till Kännedomen om ryggmärgsförändringar vid perniciös anemi, Nord. Med. Ark., Stockholm, 1896, ix, No. 7, 1.

[63] Perniciösen Anämie beobachteten Spinalerkrankungen, Arch. f. Psych., 1893, xxv, 421; Weitere Beiträge zur Kenntniss der im Verlaufe der perniciösen Anämie beobachteten Spinalerkrankungen, Deut. Ztschr. f. Nervenheilk., 1894-95, vi, 313.

[64] Casuistisches Beitrag zur Kenntniss der anatomische Befunde bei spinaler Erkrankung mit progressiven Anämie, Arch. f. Psych., 1898, xxx, 372.

[65] Die primären combiniter Strängerkrankungen des Rückenmarks, Deut. Ztschr. f. Nervenheilk., 1895, vii, 171.

[66] Ueber eine eigenthümliche durch Gefässdegenerationen hervorgerufene Erkrankung der Rückenmarks Hinterstränge, Ztschr. f. Heilk., Berlin, 1891, xxi, 247.

[67] Zur pathologischen Anatomie der Seitenstrángerkrankung bei Tabes Dorsalis, Deut. Arch. f. klin. Med., Leipzig, 1889-90, xliv, 113.

To account for the degeneration occurring especially in the posterior columns, Orr and Rows have shown that in tabetic conditions the degeneration is particularly marked at the point of entrance of the nerve roots. Also by injections of tetanus toxin and various bacterial emulsions into nerves they have demonstrated how the toxic agents ascend to the cord. They consider that the immunity of the nerves is due to the enveloping neurilemma and that only in the unprotected portion of the system where the nerve fibrils are contained in the cord, can the toxins produce any effect. It is certainly, however, somewhat difficult to apply this to either of our cases; moreover, in both of our cases the posterior roots were not altered. It seems more natural to assume a greater vulnerability to degenerative processes in certain areas of the spinal cord than in others.

In connection with these cases it has to be, to some extent, considered, just how far postmortem conditions can simulate any system lesion. These postmortem processes, however, do not produce the peculiar degenerative vacuolization nor the hyaline appearances of gliosis. In this connection the study of a series of such postmortem conditions in the cord at various intervals after removal from the body, was undertaken, with the result that system changes or appearances such as have been described were not observed.

In the consideration of the cavity formation in the lower dorsal region in Case I, there perhaps lies the one point of interest which permits of these cases being put on record. The cavity, as has been noted, was situated on the left side of the cord, between the tenth dorsal and first lumbar segments, and occupied almost exclusively the gray matter, particularly of the anterior horn. This destruction and cavity formation corresponded almost entirely to a branch of the anterior spinal artery. This vessel supplies the greater part of the gray matter, while most of the rest of the cord is nourished by the pial vessels. It was apparently a thrombosis in one of the small largest, of any necrosis of tissue. This process probably was produced in the last few hours of life. It was difficult to be exact as to the duration of the process, as no clinical symptoms had been evident. The absence of clinical symptoms is explained by the location of the lesion and by the fact that the patient was comatose for some time before death.

Several examples of cases of thrombosis of the spinal cord vessels have been mentioned by various authors (Dana, Petrén[68]), and Hawthorne[69] has advocated that many of the cerebral and ocular complications of pernicious anemia (retrobulbar neuritis, ocular paralysis, optic neuritis, etc.) are due to vascular thrombosis. The appearances, however, described by these authors, have not been quite similar to what was found in our cases. These have been, in the majority of cases, of the nature of a hemorrhagic necrosis of the gray matter, particularly of the anterior horn. Experimentally, such conditions have also been produced by aseptic emboli, by Lamy;[70] also Ehrlich and Brieger,[71] Münzer and Wiener,[72] Singer and Münzer,[73] and Spronck[74] have produced similar changes by clamping the aorta in rabbits just behind the renal artery. Singer and Münzer showed in such conditions that areas of the posterior columns may become degenerated, but in our case the degeneration in the posterior tracts, besides being bilateral, was evidently of much older date than the cavity in the gray matter in the lower dorsal region.

Bulloch[75] (1892) described, in a case of pernicious anemia, hyaline masses in the cord chiefly involving the anterior horns of the gray matter, and referred this to an exudation from the adjacent vessels. Henenberg[76] (1899) described two cases of combined sclerosis in which there were found cavities in the spinal cord. In one case the cavity was central and in the other it occupied the centre of one of the anterior horns. He considered thrombosis as the essential factor in their production.

The cavities in the spinal cord in syringomyelia, and the simple

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[68] Fall von akuter Infektionskrankheit mit Thrombose in den pialen Gefässen, etc., Nord. Med. Ark., 1808, ix, No. 7, 1.

[69] An Address on the Cerebral and Ocular Complications of Anemia and the Probable Relationship of These to Thrombosis, Lancet, 1908, ii, 857.

[70] Lésions médullaires expérimentales produites par les embolies aseptiques, Arch. de physiol. norm. et pathol., 1897, ix, 184.

[71] Ueber die Ausschaltung des Lendenmarksgrau, Ztschr. f. klin. Med., 1883, vii, Supp. Heft, 155.

[72] Beiträge zur Anatomie und Physiologie des Centralnervensystems, Arch. f. exp. Path. u. Pharmak., 1895, xxxv, 113.

[73] Beiträge zur Anatomie des Centralnervensystem, Akad. d. Wissenschaften, Wien, Denkschriften, 1890, lvii.

[74] Contribution à l'étude expérimentale des lésions de la moelle épinière déterminées par l'anémie passagère de cet organe, Arch. de phys. norm. et path., 1888, 389.

[75] Hyaline Degeneration in the Spinal Cord, Brain, 1892, xv, 411.

[76] Beitrag zur Kenntniss der combinite Strängdegeneration, sowie der Höhlenbildung im Rückenmark, Arch. f. Psych., 1889, xxxii, 550.